Transplantation (for MPN) 2023

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Outline

- Indications
- Set and setting
  - Patient attitude
  - Donor choice
- Outcome
- GVHD prevention

Indications

- Marrow failure/cytopenias
- Disease “acceleration”
- Leukemic transformation
- Failure of non-transplant modalities

Risk Classification

- **Anemia**
- **WBC > 25,000**
- **Myeloblasts in blood**
- **Age (> 65 years)**
- **Symptoms**

DIPSS

- **Abnormal chromosomes**
- **Low platelet count**
- **Requiring transfusions**

DIPSS plus

- **Mutations**
  - ***JAK2, MPL1, CALR***
  - ***ASXL1, p53, etc***

MIPSS **and more**

Splenomegaly pre-Transplant

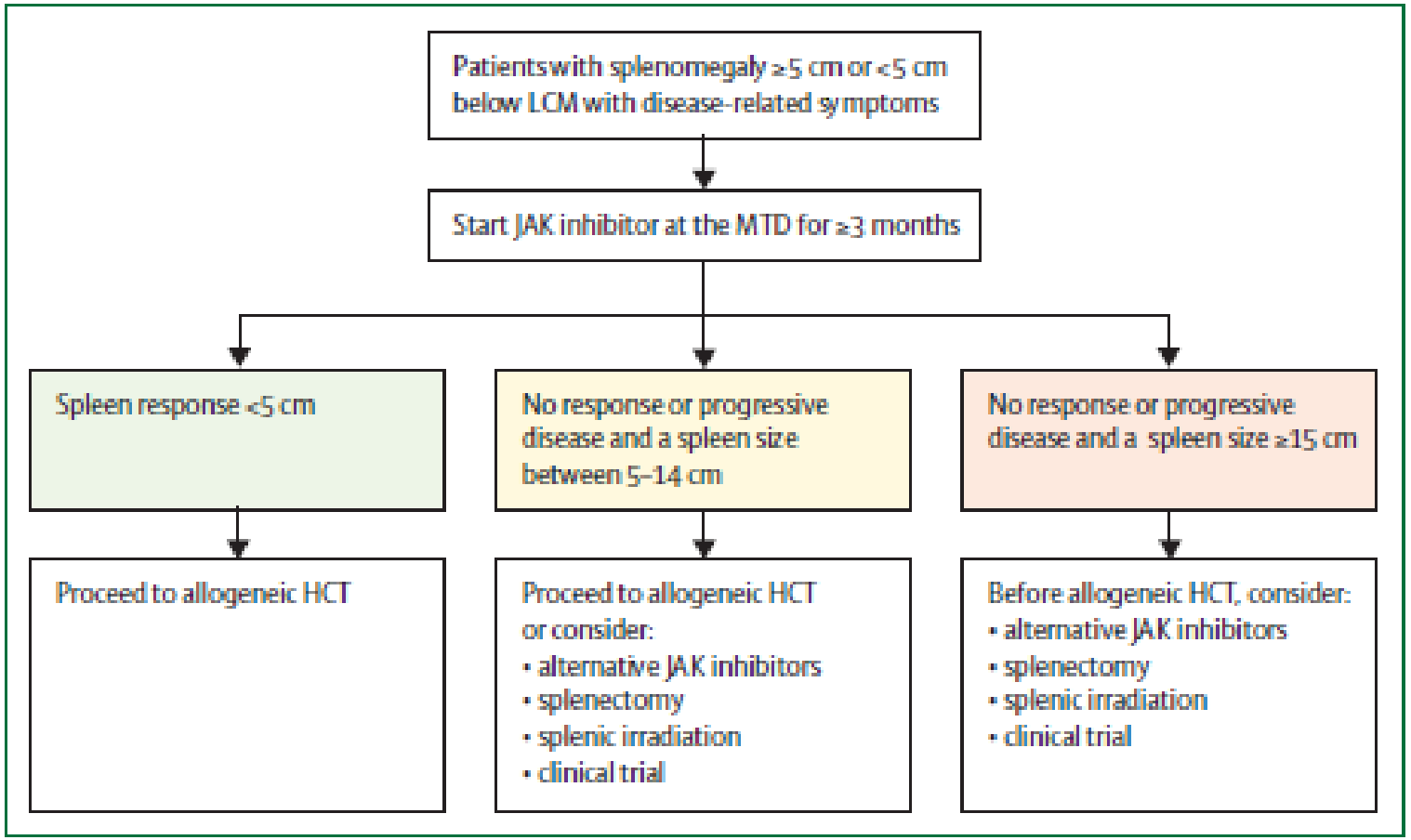
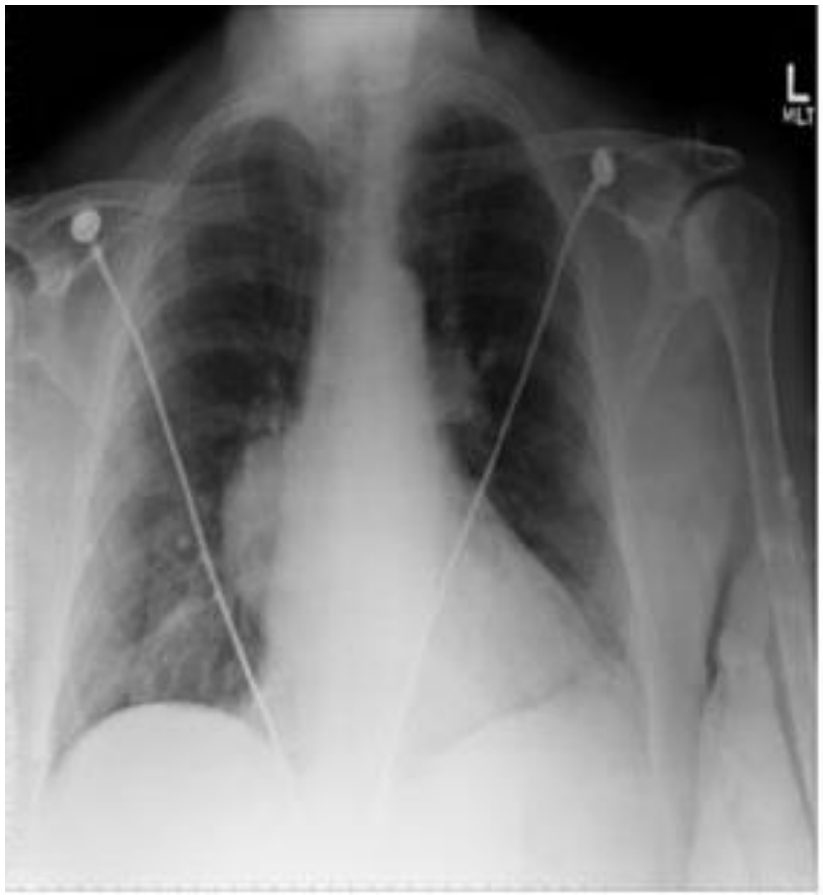


Figure 2: **Flowchart for managing myelofibrosis candidates for transplantation with splenomegaly**
HCT=haematopoietic cell transplantation. LCM=left costal margin. MTD=maximum tolerated dose.

N. Polverelli et al, Lancet Haematology 2022

“Bone marrow” in the Lung



J.Wang & D.I.Kuperman, Ann.Hematol. 92: 1559, 2013

Set and Setting

Clonal Hematopoiesis and Risk of Myeloid Neoplasia*

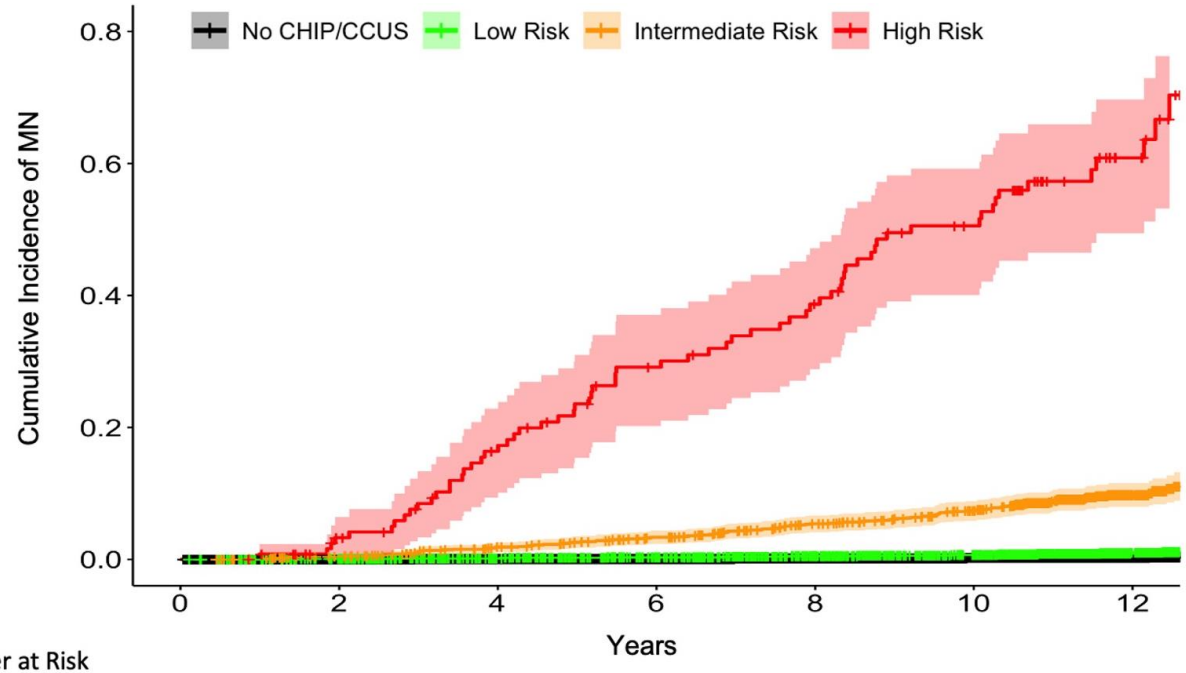
Table 1. CHRS risk categories and Myeloid Neoplasia outcomes in hematology patient cohorts

	DFCI/BWH CHIP/CCUS Patient Cohort				Pavia CCUS Patient Cohort			
	Total	Low Risk	Intermediate Risk	High Risk	Total	Low Risk	Intermediate Risk	High Risk
Patients (N %)	646 (100%)	170 (26.3%)	285 (64.1%)	191 (29.6%)	99 (100%)	14 (14.1%)	52 (52.5%)	34 (34.3%)
MN events	31	1	7	23	34	2	12	20
MN event rate	4.8%	0.588%	2.46%	15.2%	34.3%	14.3%	23.1%	58.8%
HR (95% CI)	--	ref	4.53 (0.556, 36.9)	30.6 (4.09, 228)	--	ref	2.87 (0.631, 13.1)	8.803 (1.93, 40.1)
	Concordance (s.e.) = 0.788 (0.039)				*Concordance (s.e.) = 0.727 (0.039)*			

Whole genome sequencing data from 193,743 individuals in the UK Biobank
Pathogenic gene variants in 11,337 (5.85%) who met CHIP/CCUS criteria
Adding sex, smoking Hx, prior cancer → CHRS

L.D. Weeks et al, ASH 2022, Abstract 926

CHIP/CCUS and Risk of Myeloid Malignancy



Number at Risk

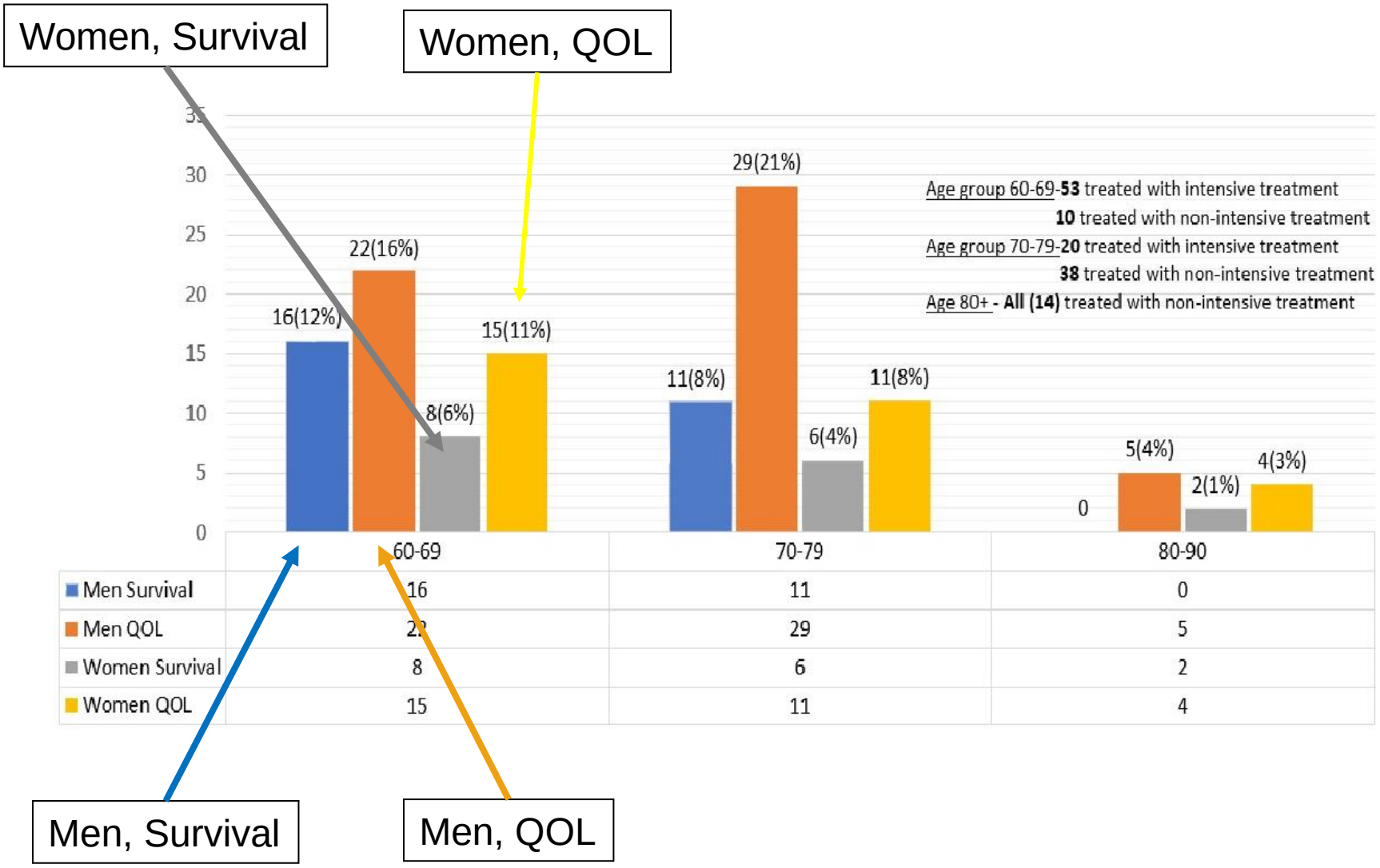
Time(years)	0	2	4	6	8	10	12
High-risk	128	114	94	75	63	46	16
Int-risk	1277	1251	1200	1156	1090	1031	372
Low-risk	9932	9876	9742	9620	9463	9275	3735
No CHIP/CCUS	182406	181674	180407	178734	176174	174455	72254

Factors included in CHRS:
DNMT3A mut;
high risk muts.;
>1 mut.;
CCUS vs CHIP;
patient age;
RBC indices

L.D. Weeks et al, ASH 2022, Abstract 926

Patient Goals and Treatment Intensity

N=135, AML

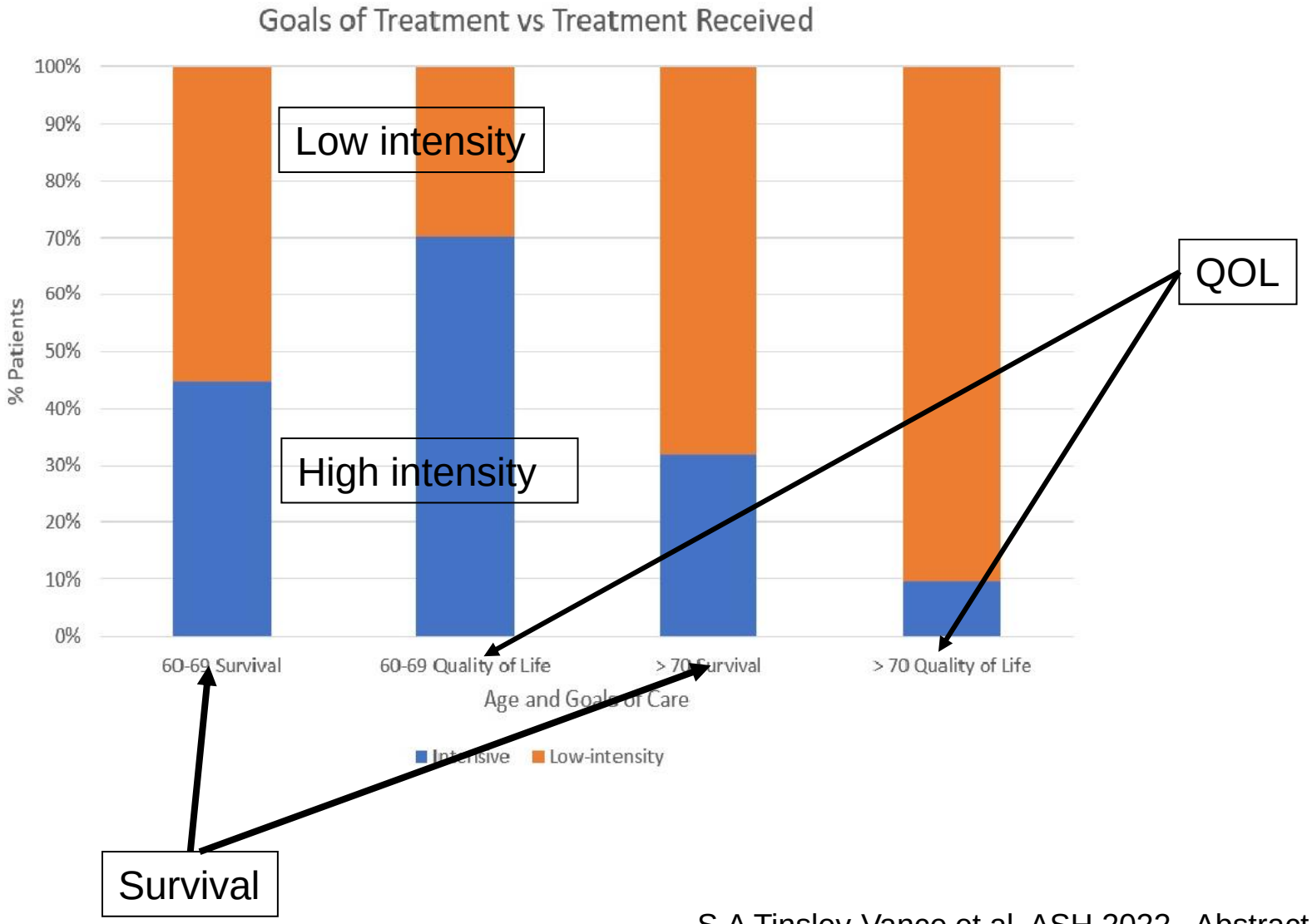


	60-69	70-79	80-90
Men Survival	16	11	0
Men QOL	22	29	5
Women Survival	8	6	2
Women QOL	15	11	4

S.A Tinsley-Vance, ASH 2022, Abstract 3631

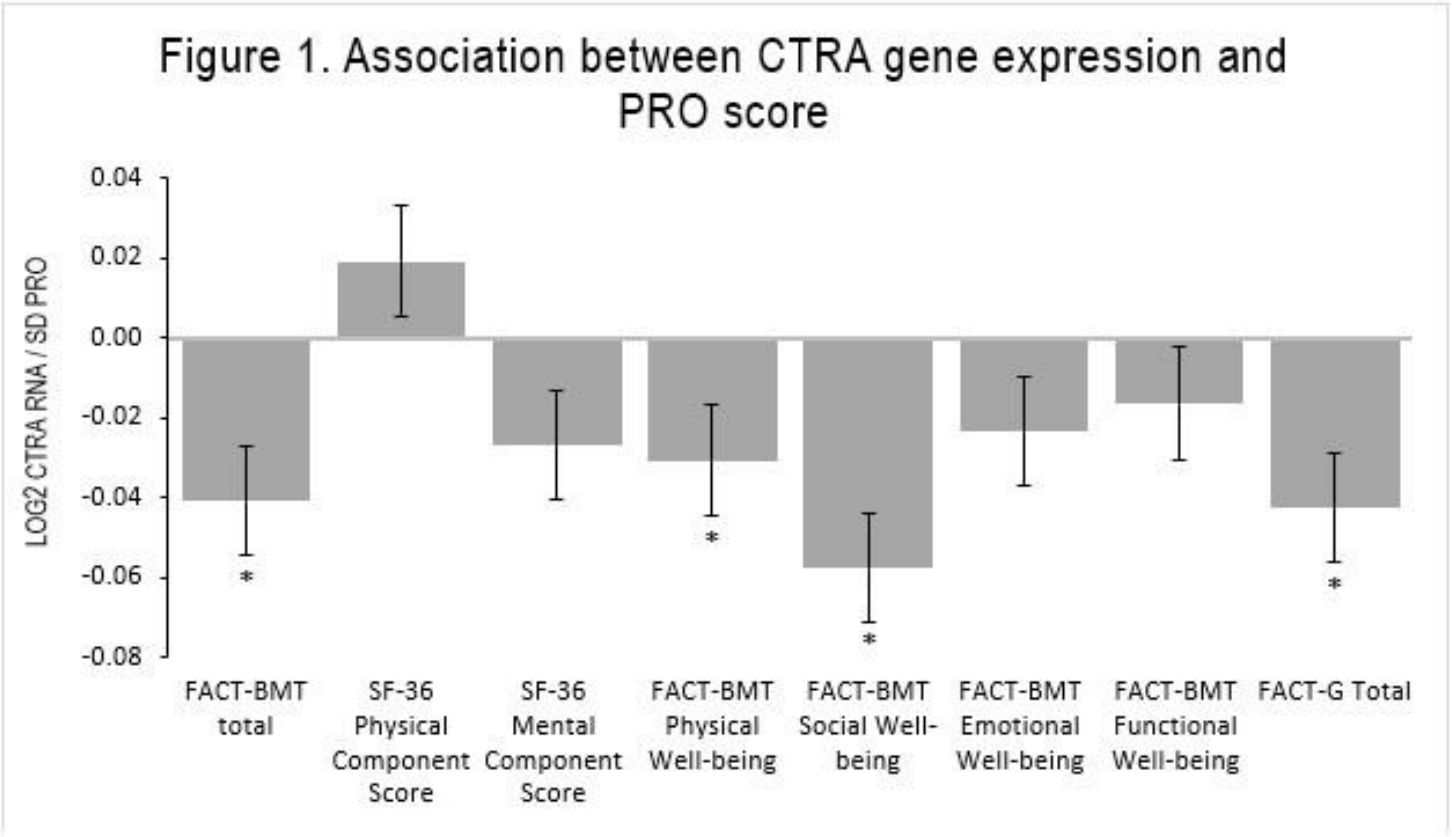
Patient Goals and Treatment Intensity

N=135, AML



S.A Tinsley-Vance et al. ASH 2022,, Abstract 3631

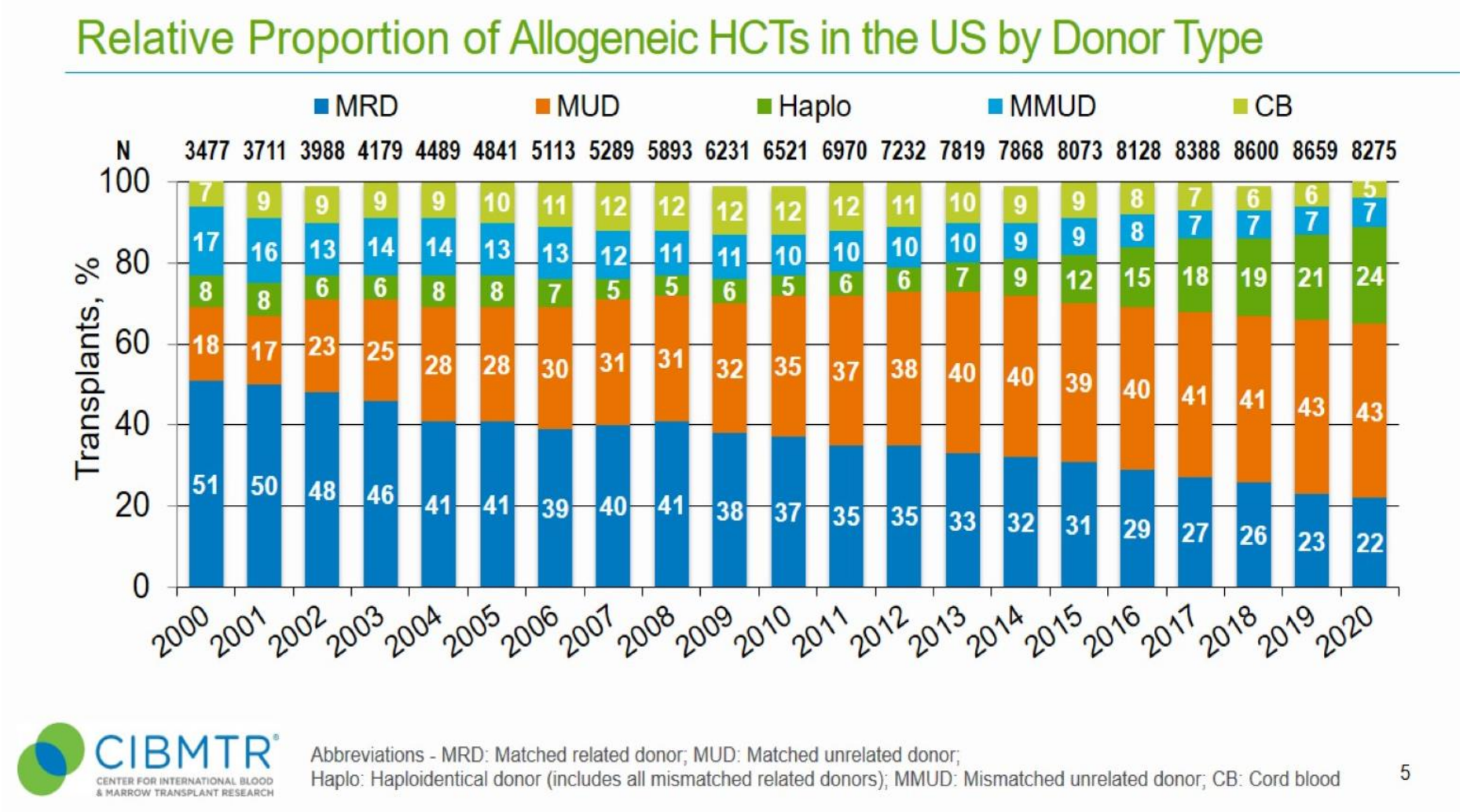
Lower CTRA* score – Better Well-being



*CTRA= conserved transcriptional response to adversity,
A genomic biomarker including increased expression of
Pro-inflammatory genes and decreased expression of
Innate anti-viral genes
PRO= Patient reported outcome

M. Taylor et al, ASH 2022,, Abstract 375

Donor Selection over two decades



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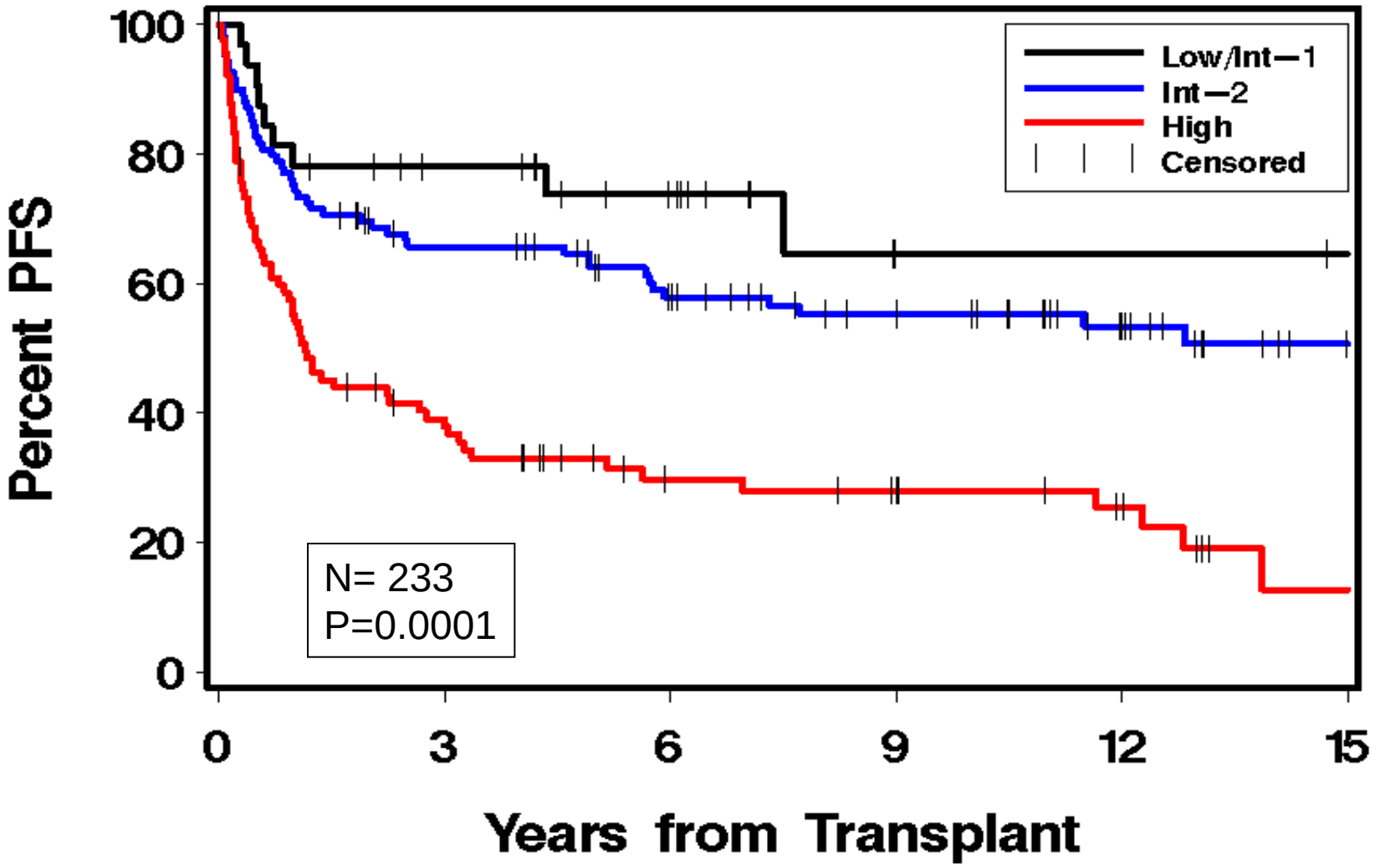
Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

Outcome

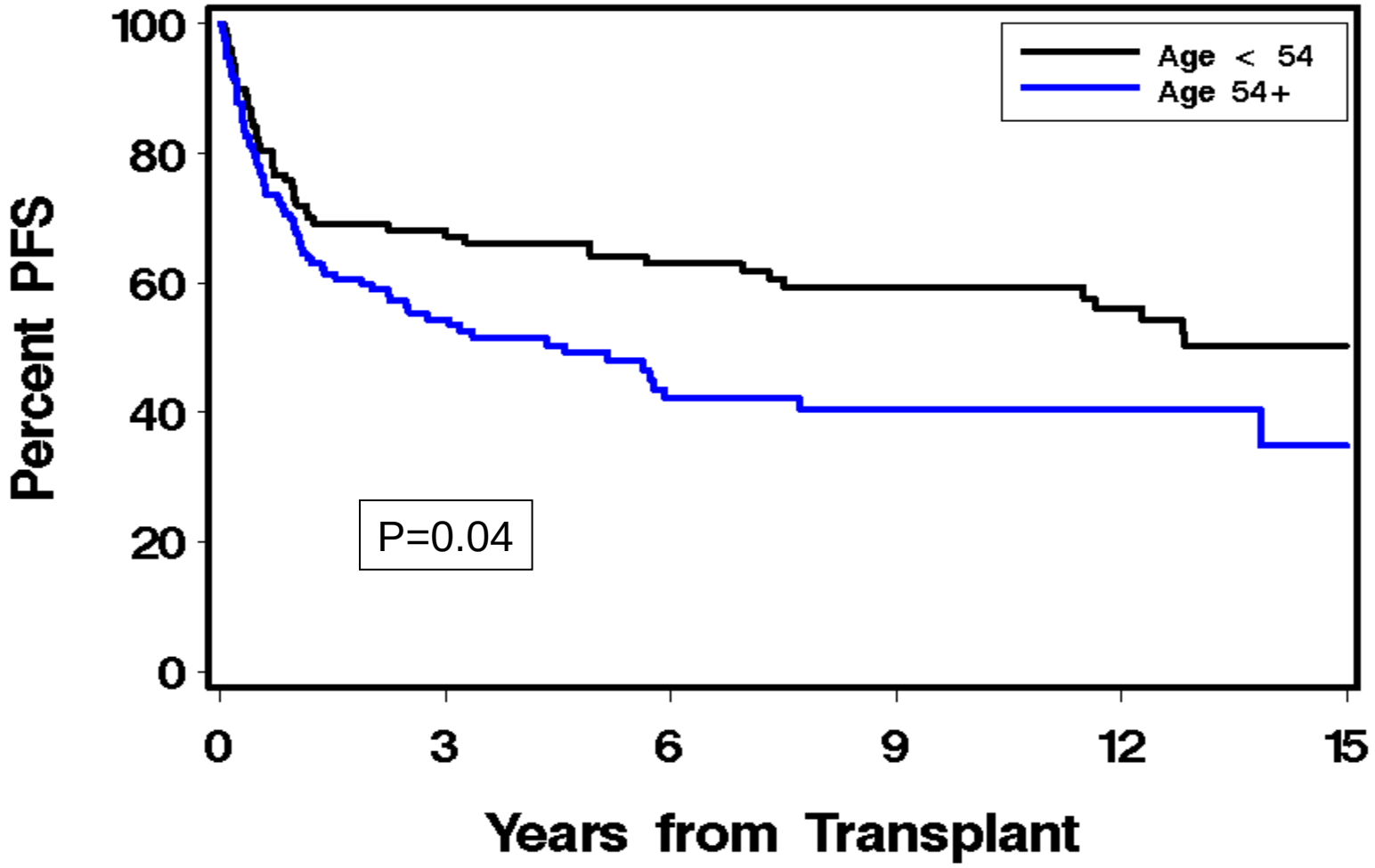
Progression-free survival by DIPSS *plus*

(all regimens)



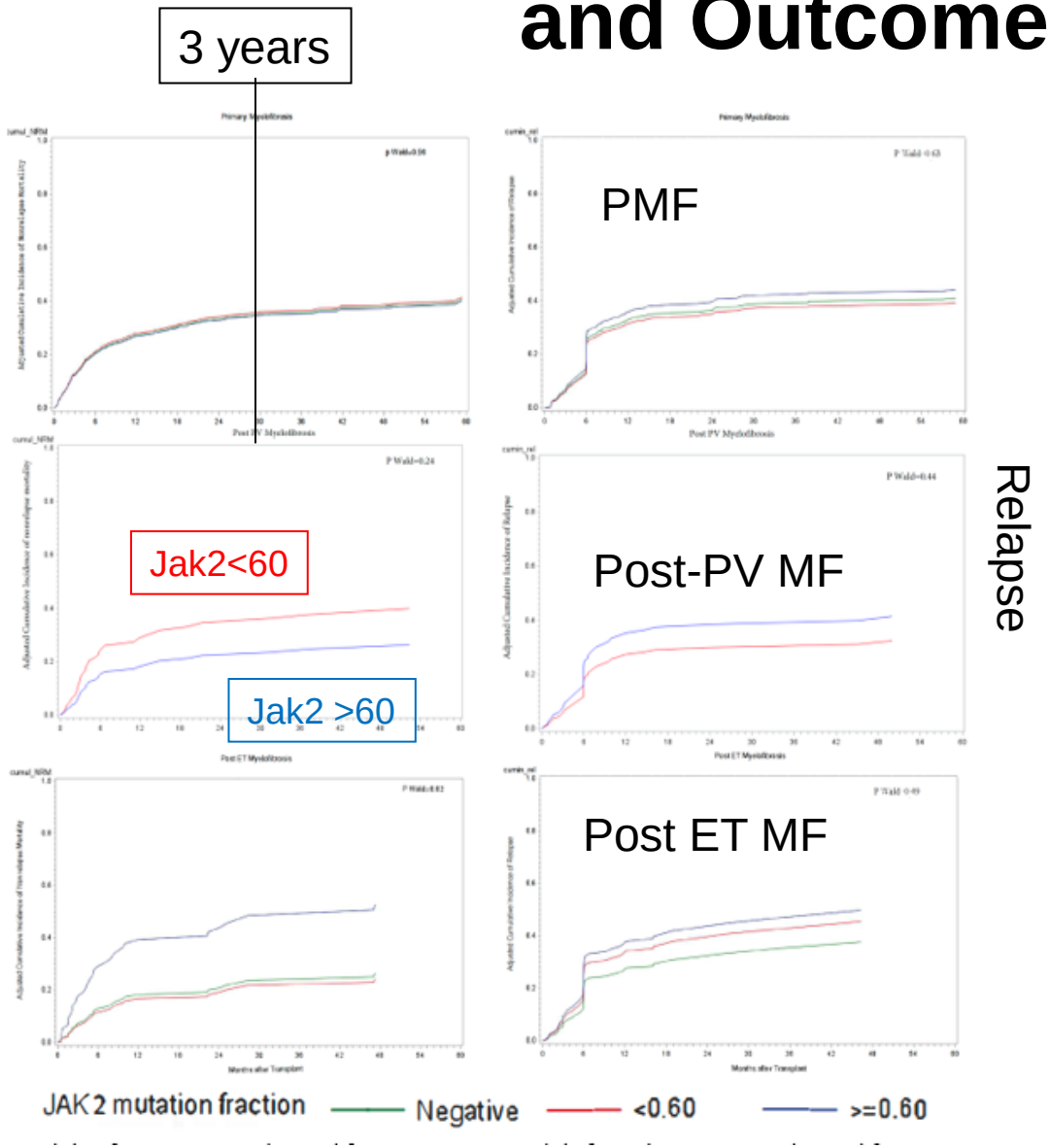
Samuelson B et al BBMT 24:386, 2017

Age and Survival



Samuelson B et al BBMT 24:386, 2017

Primary vs secondary MF, Allele Burden and Outcome



N= 924
Role of JAK2 (V617F) and Mosaic chrom. alt.

M.Rafati, ASH 2022, Abstract 373

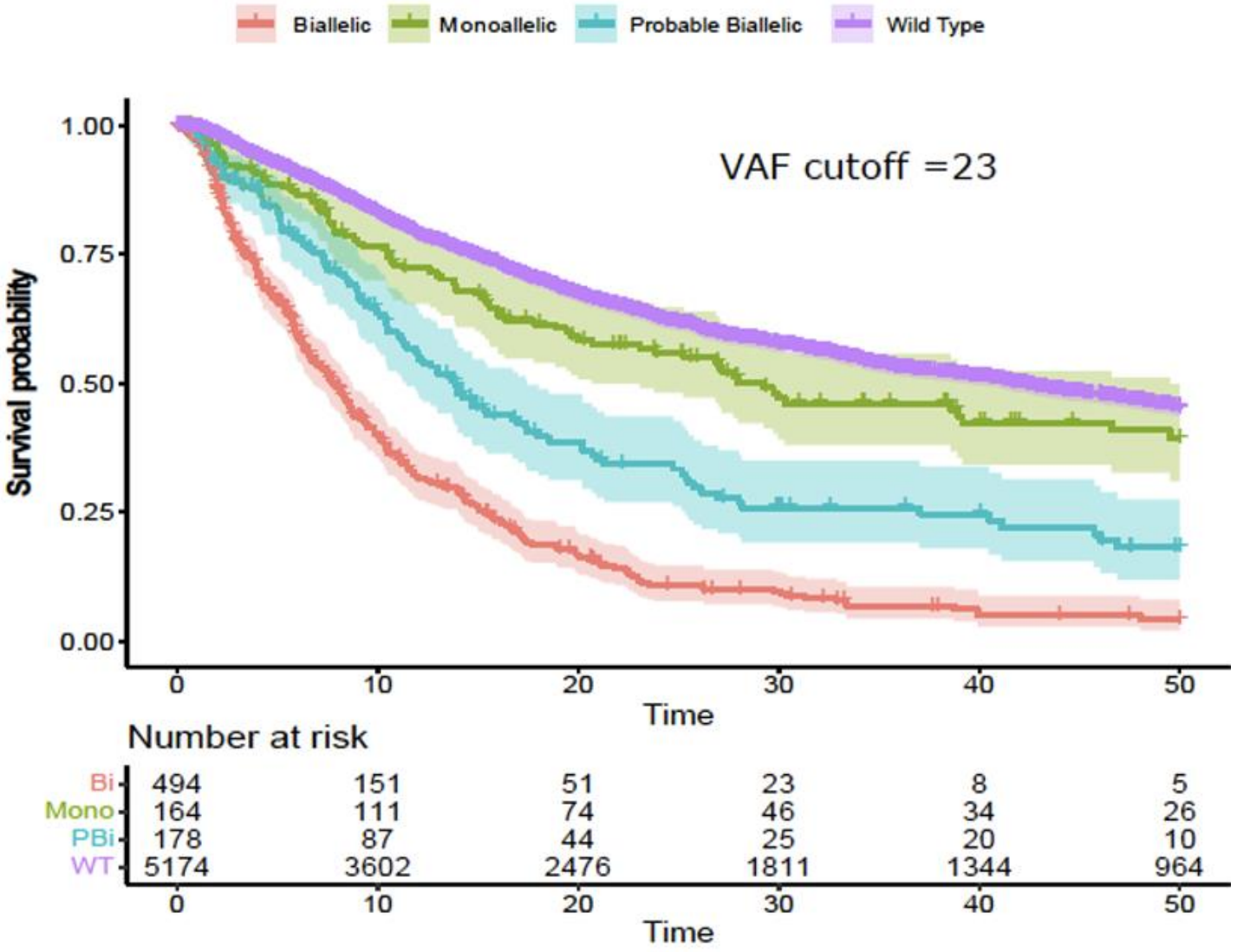
$TP53^{mut}$, complex Karyotype and Outcome

	N	VAF	Med Age (ys)	f/u (ys)	Med OS(ys)	Relapse (at 6ys)
Number	349					
TP53 mut	49* (13%)	3-97%	56	5.8	1.5	35%
TP53 wt	300		57	9.2	13.5	2%
Complex karyotype	36 (10%)					
Mut+complex	11 (29%)				1.9	
Other					13.59	

- N=16 multi-hit;
- 7 centers

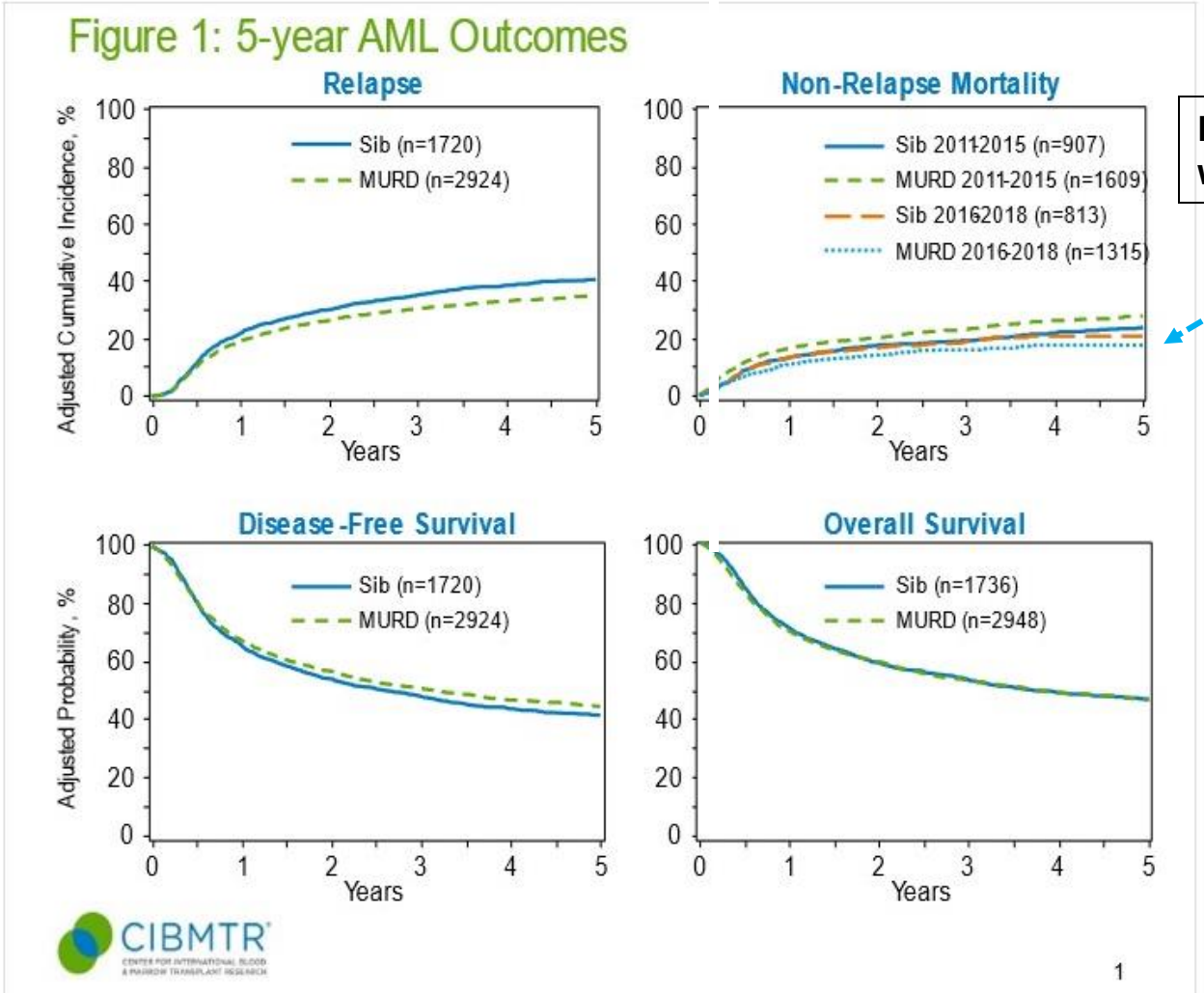
TP53 Alleles and Survival

(various myeloid malignancies)



W.Bahaj et al Ash 2022 Abstract # 857

Older Siblings vs Younger Unrelated Donors



Decrease in NRM with URDs in 2016-2019

N=4684 AML
HLA= sibs 1736; donors **≥ 50 ys**
HLA=URD 2948; donors **≤ 35 ys**

M. Bilal Abid et al, ASH 2022, Abstract # 374

Increased GVL Effect with younger URDs

Table 1: Multivariable analyses of the impact of donor age (MUD vs MSD) on alloHCT outcomes in AML patients

Outcome	No. of patients	HR (95% CI)	P-value
Relapse:			
MSD	1720	1.00 (Reference)	***0.005***
MUD	2924	***0.86*** (0.77-0.96)	
NRM 2011-2015:			
MSD	907	1.00 (Reference)	***0.016***
MUD	1609	**1.24** (1.04-1.49)	
NRM 2016-2018:			
MSD	813	1.0 (Reference)	**0.017**
MUD	1315	**0.78** (0.64-0.96)	
DFS:			
MSD	1720	1.0 (Reference)	0.073
MUD	2924	0.92 (0.85-1.01)	
OS:			
MSD	1736	1.0 (Reference)	0.607
MUD	2948	1.02 (0.94-1.12)	
OS (Center effect):			
MSD	1736	1.0 (Reference)	0.653
MUD	2948	1.02 (0.93-1.12)	

All patients

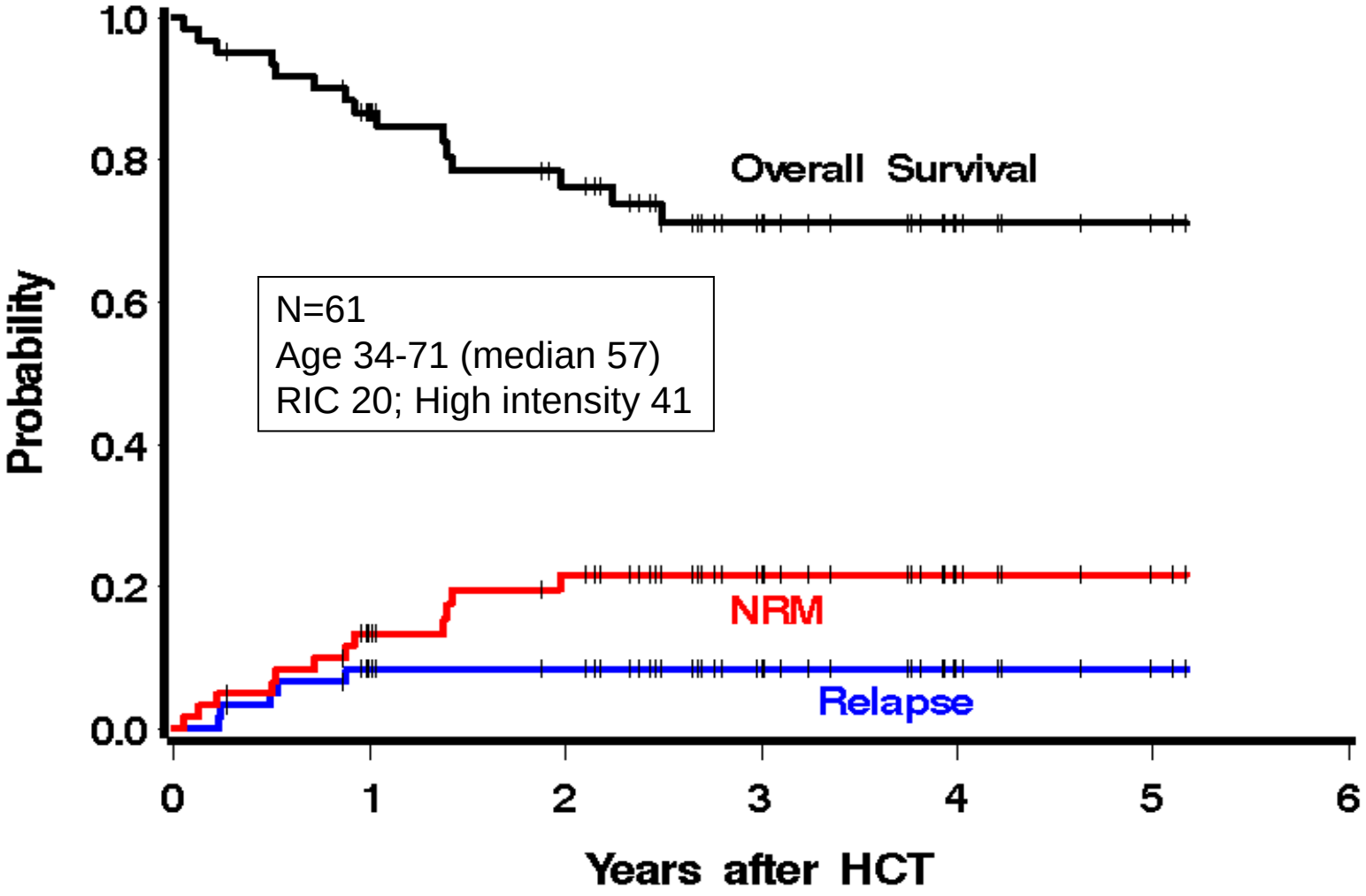
Table 2: 5-year adjusted CI of relapse and NRM and survival probability in AML patients undergoing alloHCT

Outcome	No. of patients at risk	% (95% CI)	P-value
Relapse:			
MSD	327	41% (38%-43%)	***0.003***
MUD	557	35% (33%-37%)	
NRM 2011-2015:			
MSD	304	24% (20%-27%)	***0.045***
MUD	530	28% (25%-30%)	
NRM 2016-2018:			
MSD	23	20% (17%-24%)	0.147
MUD	27	17% (15%-20%)	
DFS:			
MSD	327	41% (38%-43%)	***0.045***
MUD	557	44% (42%-46%)	
OS:			
MSD	287	47% (44%-49%)	0.953
MUD	523	47% (45%-49%)	

Adjusted

M. Bilal Abid et al, ASH 2022, Abstract # 374

Tx for MPN -Pre-Tx Ruxolitinib

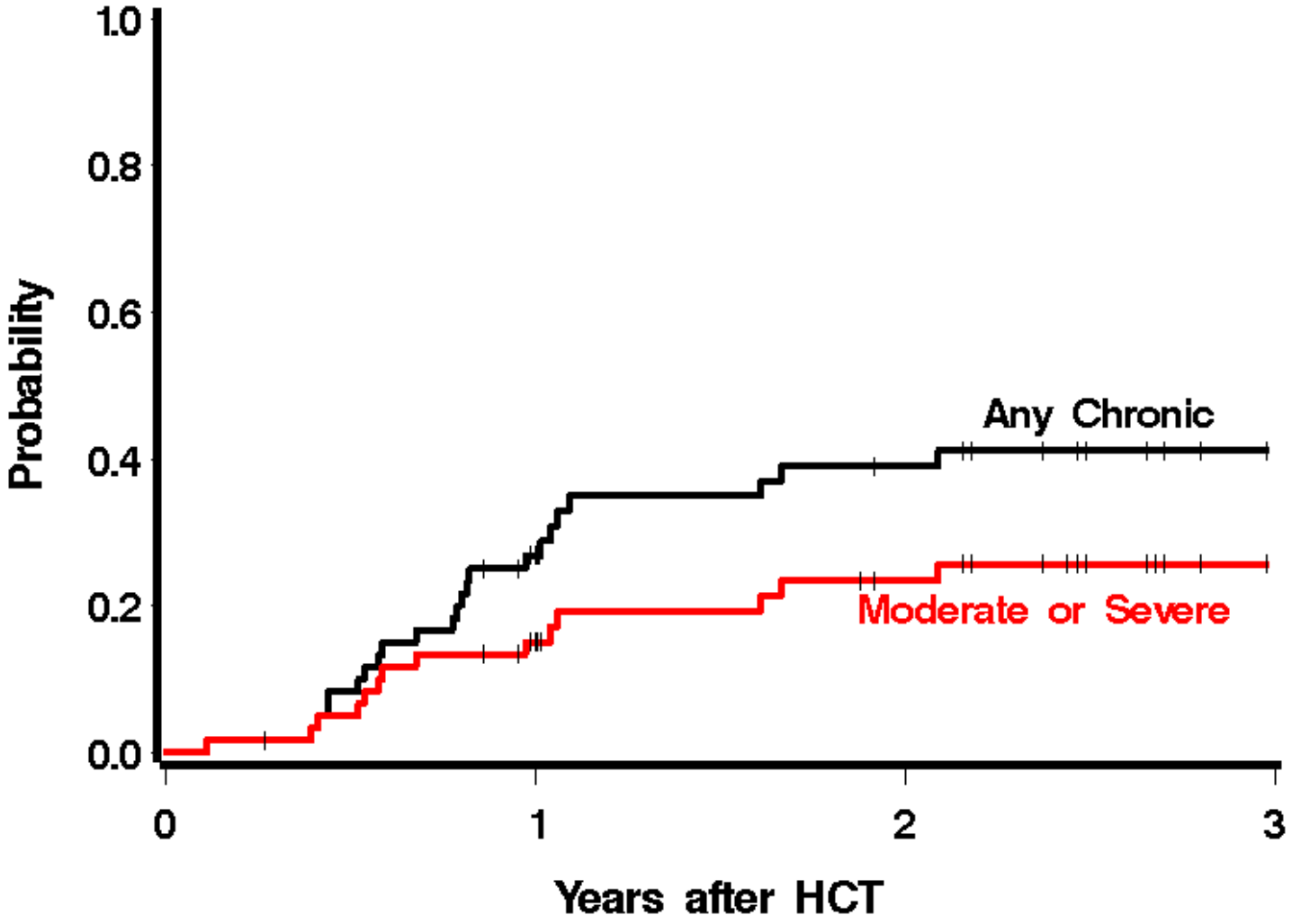


R. Salit et al, unpublished

GVHD Prevention

Transplant for MPN – Chronic GVHD

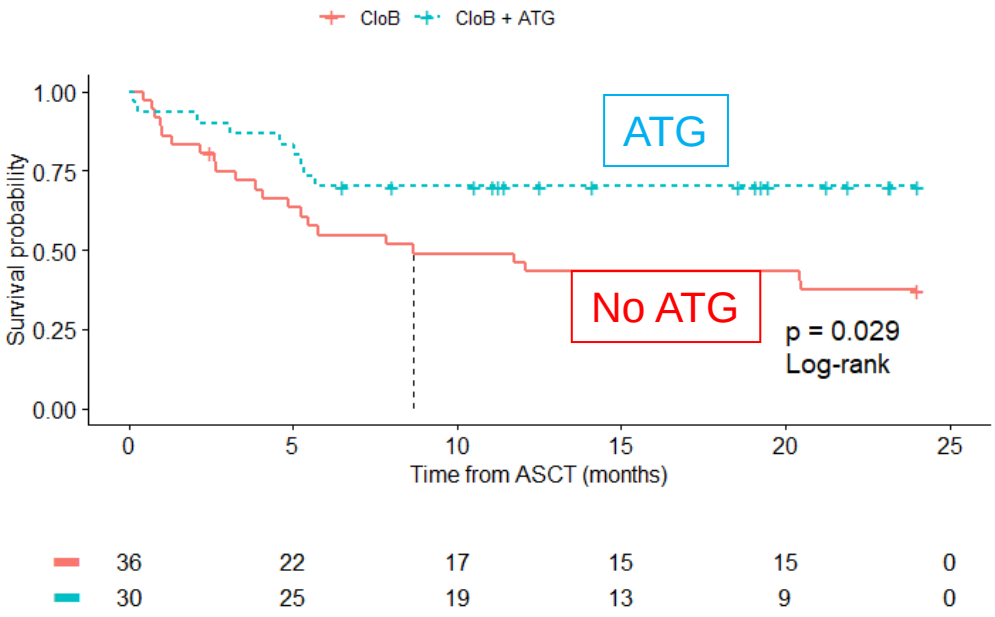
with pre-Tx Jak2 inhibitor



R. Salit et al, unpublished

Benefit of ATG

Figure 1. GRFS according to conditioning.



Conditioning:
Clofarabine 30/m^2/d d-6 to-2
CY 14.5/kg/d d-6,-5; CY50 d+3, +4
+/-ATG 2.5mg/kg d-2
Post Tx CSP+MMF

PBSC; various myeloid malignancies

Maxime Jullien, ASH 2022, Abstract 46 88

Benefit of ATG

Table 1. Patient Characteristics according to conditioning.

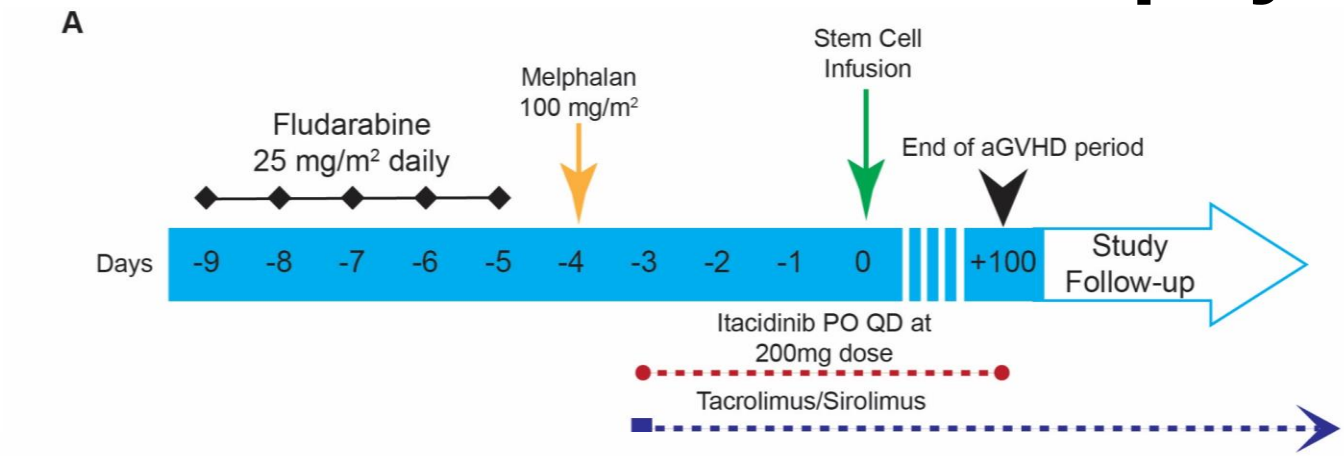
	CloB	CloB +ATG	p-Value
	n = 36	n = 30	
Age	61.3[31.9-71.3]	59.5[34.6-73.6]	0.919
Gender (female)	17 (47.2%)	9 (30%)	0.241
Disease			0.974
AML	17 (47.2%)	15 (50%)	
MDS	10 (27.8%)	8 (26.7%)	
other	9 (25%)	7 (23.3%)	
DRI			**0.03**
Low/inter	23 (63.9%)	27 (90%)	
High	13 (36.1%)	3 (10%)	
HCT-CI	3[0-7]	3[0-7]	0.808
Previous SCT			0.235
no	25 (69.4%)	26 (86.7%)	
autologous	4 (11.1%)	1 (3.3%)	
allogeneic	7 (19.4%)	3 (10%)	
Donor			0.21
haploidentical	27 (75%)	27 (90%)	
matched	**9 (25%)**	**3 (10%)**	

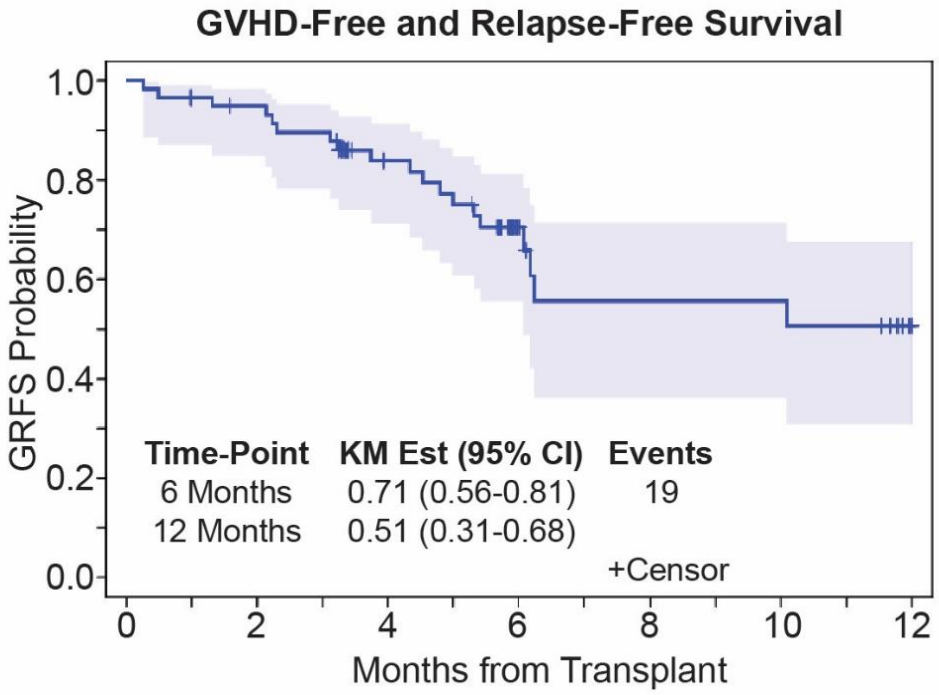
Numbers are given as Median/Count (range/%).

Conditioning:
Clofarabine 30/m^2/d d-6 to-2,CY 14.5/kg/d d-6,-5; CY50 d+3, +4
+/-ATG 2.5mg/kg d-2
Post Tx CSP+MMF
PBSC; various myeloid malignancies

Maxime Jullien, ASH 2022,, Abstract 46 88

Itacitinib for GVHD Prophylaxis

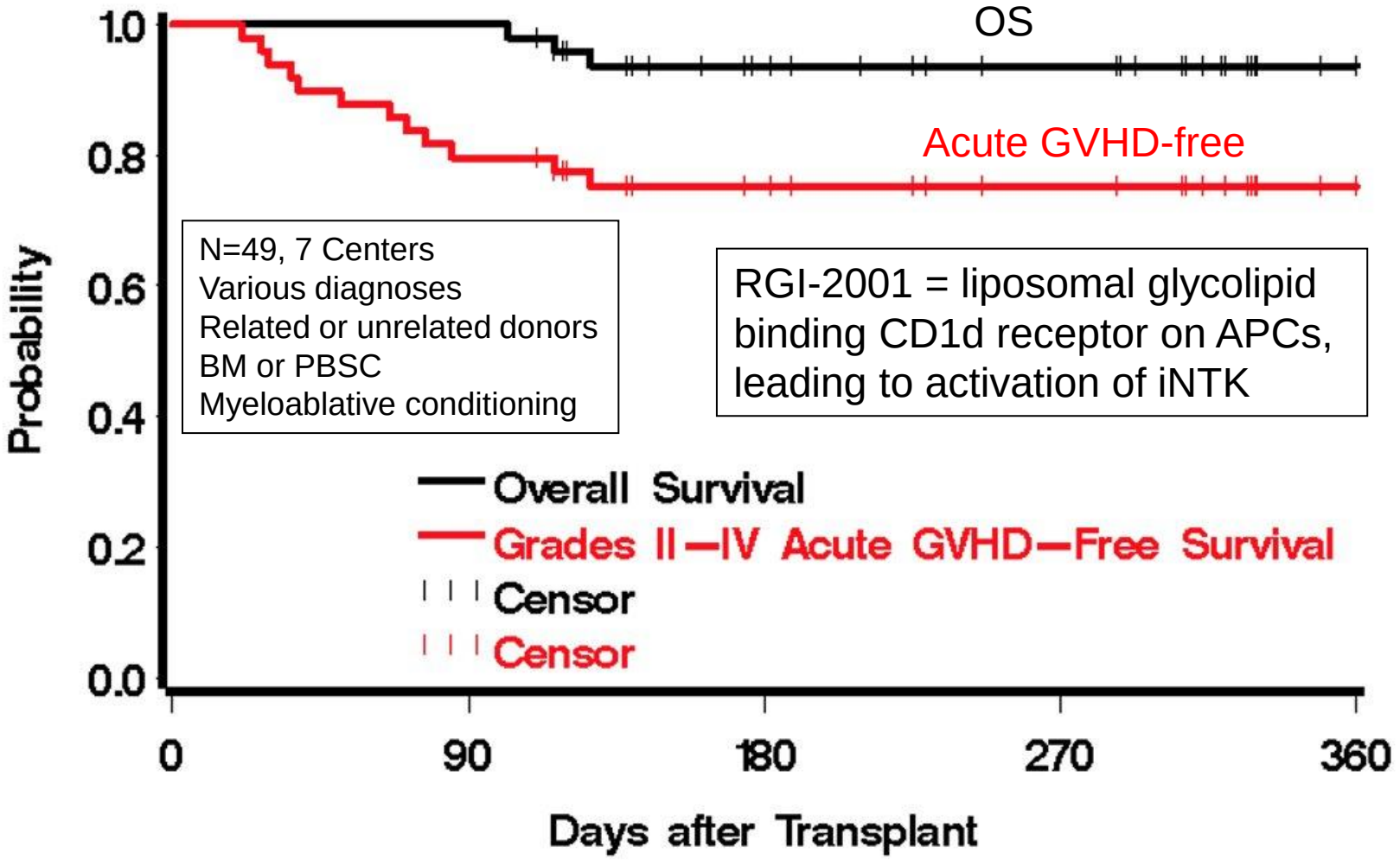




N=59, AML, MDS, MPN
Age 23-75; HCT-CI 0-1;
Acute GVHD 2-4 = 10%
Relapse N=8

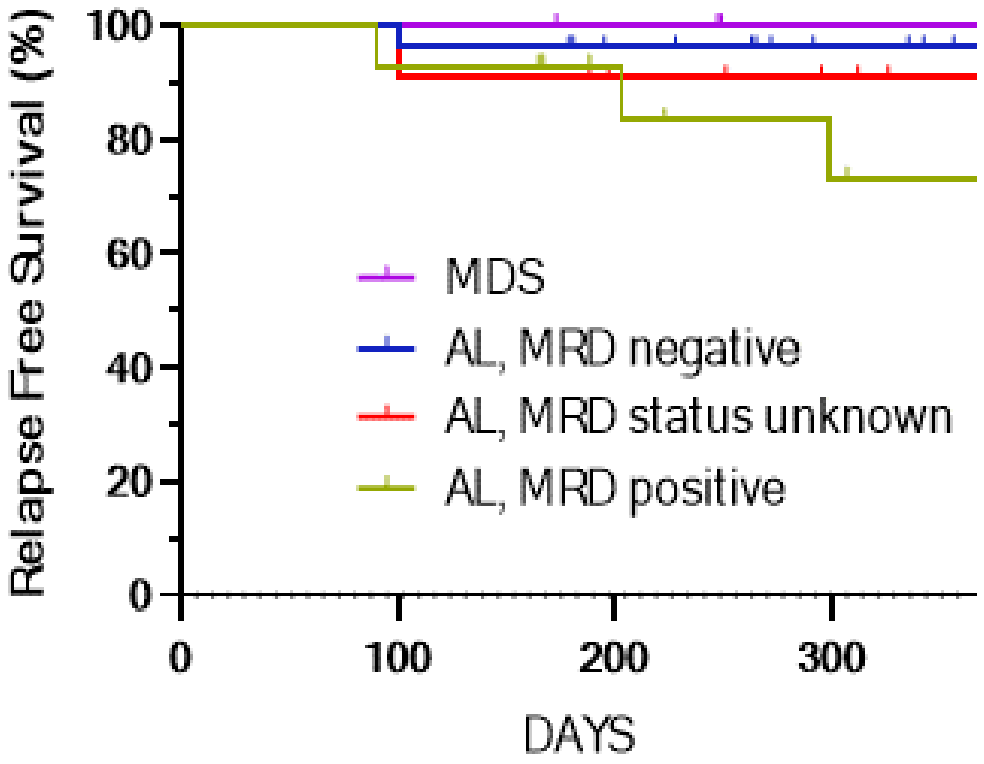
Haris Ali et al, ASH 2022, Abstract # 772

RGI-2001 and GVHD



Yi-Bin Chen et al, ASH 2022, Abstract #774

ORCA T cells* and RFS



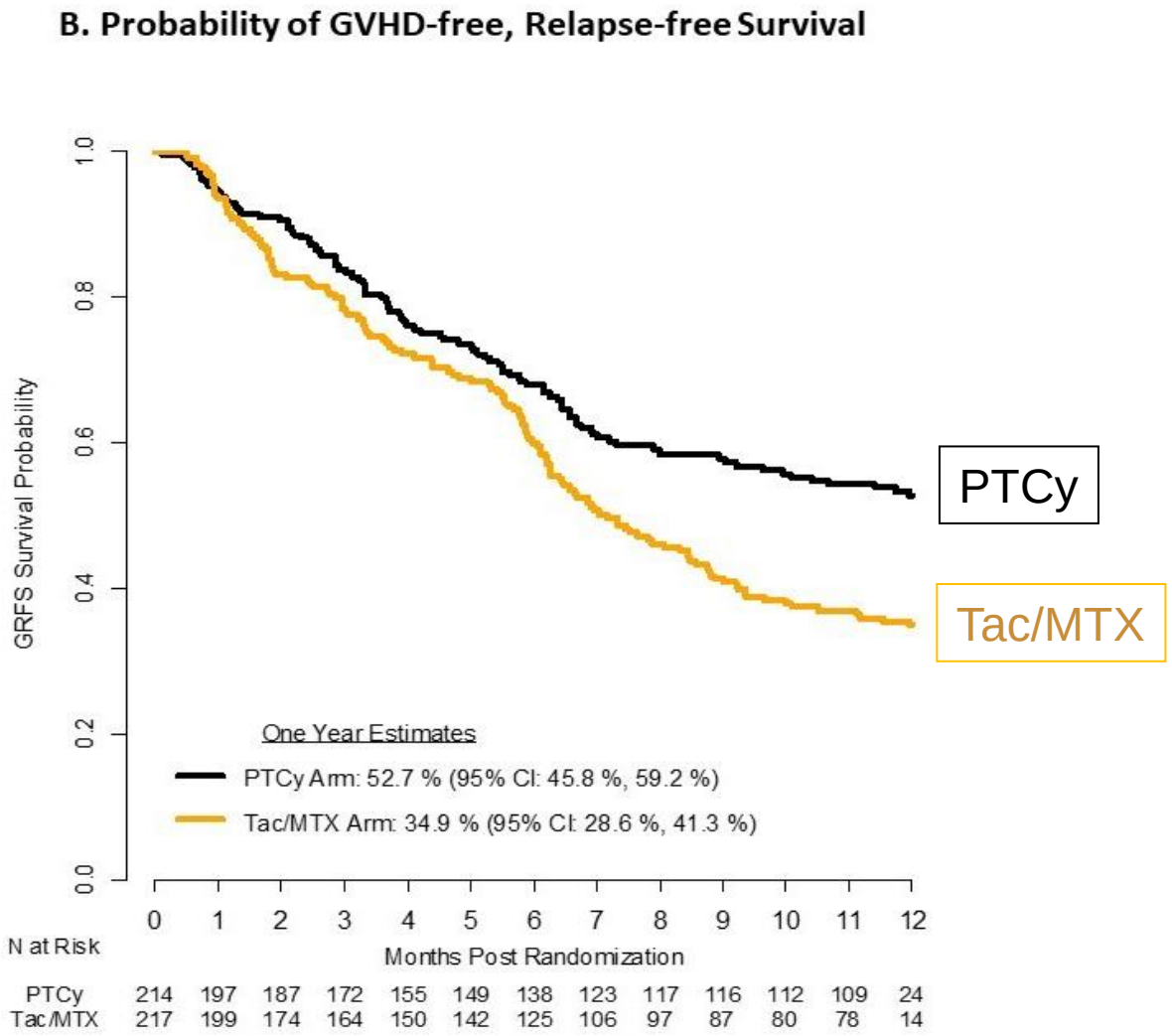
N=180
Age 19-69
Related or unrelated donors
Myeloablative conditioning
(BU or TBI based)
Tacrolimus or sirolimus
PBSC

* Allogeneic stem and immune cells that leverage Tregs

E. Oliai et al , ASH 2022, Abstract 265

Post-Transplant CY vs Tac/MTX

(BMT-CTN trial 1703)



Sh. Holtan et al, ASH 2022, Abstract # LBA4

Post-Transplant CY vs Tac/MTX

(BMT-CTN trial 1703)

A. Patient Characteristics

	Treatment Arm		
	PTCy/Tac/MMF	Tac/MTX	All
	(N=214)	(N=217)	(N=431)
Demographic Variable	N (%)	N (%)	N (%)
Gender			
Male	134 (62.6%)	126 (58.1%)	260 (60.3%)
Female	80 (37.4%)	91 (41.9%)	171 (39.7%)
Age (years)			
Mean (SD)	64.2 (8.5)	64.5 (8.9)	64.3 (8.7)
Median (Range)	66.1 (20.7, 78.6)	66.3 (26.3, 77.4)	66.3 (20.7, 78.6)
Karnofsky / Lansky Performance Score			
At least 90	106 (49.5%)	108 (49.8%)	214 (49.7%)
Less Than 90	108 (50.5%)	109 (50.2%)	217 (50.3%)
Primary Disease			
Acute lymphoblastic leukemia (ALL)	12 (5.6%)	27 (12.4%)	39 (9.0%)
Acute myelogenous leukemia (AML)	107 (50.0%)	100 (46.1%)	207 (48.0%)
Biphenotypic leukemia	1 (0.5%)	1 (0.5%)	2 (0.5%)
Chronic myelogenous leukemia (CML)	6 (2.8%)	5 (2.3%)	11 (2.6%)
Myelodysplastic syndrome (MDS)	63 (29.4%)	65 (30.0%)	128 (29.7%)
Lymphoma (all subtypes)	23 (10.7%)	17 (7.8%)	40 (9.2%)
Disease Risk Index			
Low	19 (8.9%)	21 (9.7%)	40 (9.3%)
Intermediate	125 (58.4%)	125 (57.6%)	250 (58.0%)
High / Very High	70 (32.7%)	71 (32.7%)	141 (32.7%)
Hematopoietic Cell Transplant - Comorbidity Index			
<4	164 (76.6%)	154 (71.0%)	318 (73.8%)
4+	40 (18.7%)	55 (25.3%)	95 (22.0%)
Missing/Unknown	10 (4.7%)	8 (3.7%)	18 (4.2%)
Donor Type and HLA Matching			
Related donor 6/6	60 (28.0%)	68 (31.3%)	128 (29.7%)
Unrelated donor 7/8	7 (3.3%)	8 (3.7%)	15 (3.5%)
Unrelated donor 8/8	147 (68.7%)	141 (65.0%)	288 (66.8%)
Conditioning Regimen			
Fludarabine/Busulfan	56 (26.2%)	61 (28.1%)	117 (27.1%)
Fludarabine/Melphalan	122 (57.0%)	123 (56.7%)	245 (56.8%)
Fludarabine +/- Cyclophosphamide +/- TBI	30 (14.0%)	29 (13.4%)	59 (13.7%)
Missing/Unknown	6 (2.8%)	4 (1.8%)	10 (2.3%)
Planned Post-Transplant Maintenance Therapy			
No	159 (74.3%)	170 (78.3%)	329 (76.3%)
Yes	55 (25.7%)	47 (21.7%)	102 (23.7%)

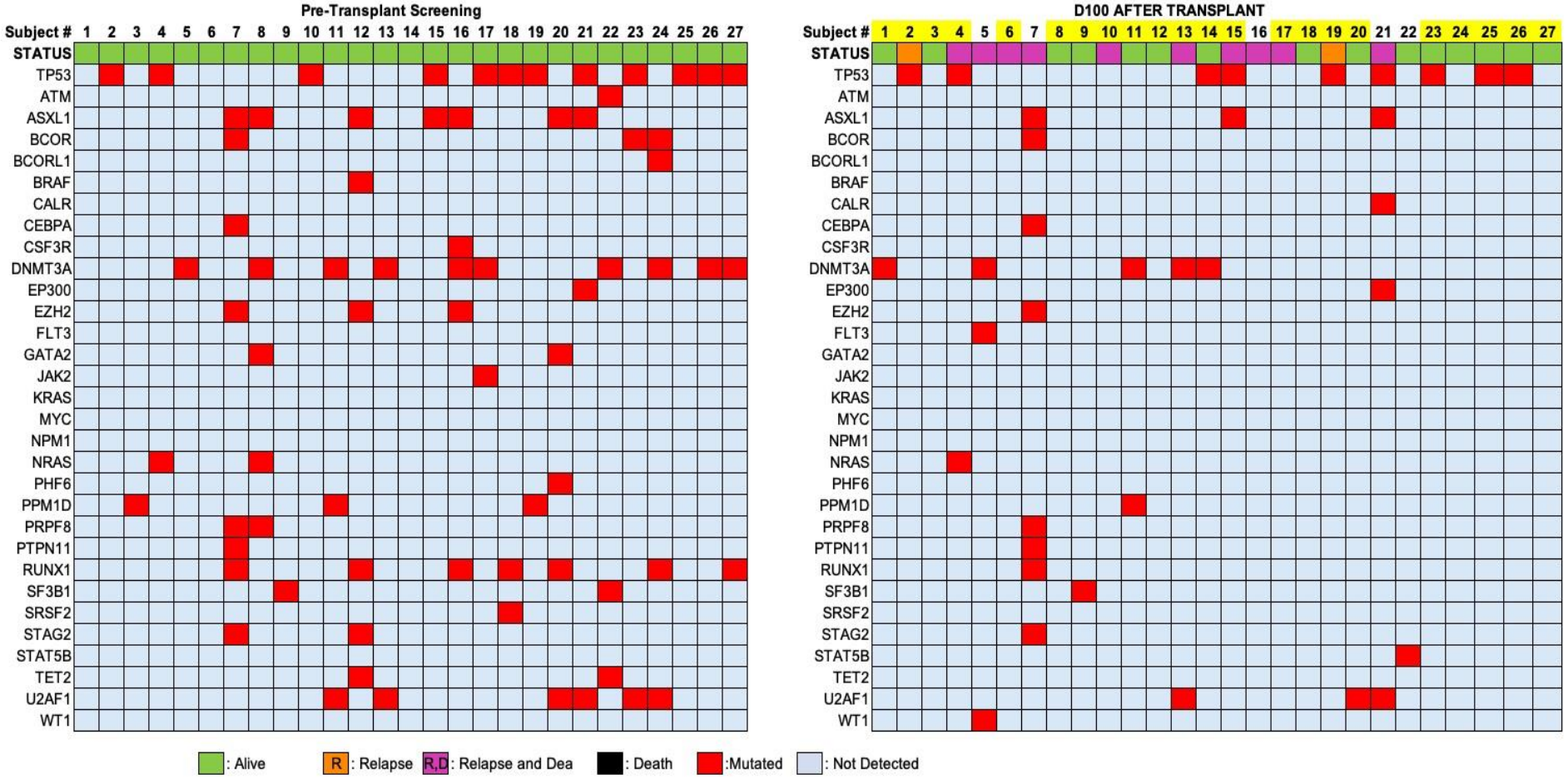
ASH 2022, Abstract # LBA4

Venetoclax+Azacitidine Maintenance

- N=27 (22)
- High risk AML, MDS and MDS/MPN; phase 1
- Conditioned with
  - Venetoclax (Ven) 400, days -8 to -2
  - Fludarabine 30/m^2/d, days -5 to -2
  - Busulfan iv, 0.8 mg/kg bid
- PBSC from 8/8 HLA matched donor, day 0
- Tacrolimus + MTX
- Maintenance between d 42 and d90
  - Ven400 d1-14
  - Aza 36mg/m^2 d1 to d5
  - Cycles of 42 or 28 days

JS Garcia, ASH 2022, Abstract 377

Mutations pre- and post-Tx



22 received maintenance (venetoclax+azacitidine)
1 year PFS/OS = 65%/79%
NRM = 0%
Relapse= 43%

JS Garcia, ASH 2022, Abstract 377

Summary

- **There is progress**
- **JAK2 inhibitors are beneficial pre- and post-Tx**
- **GVHD prevention has been improving**
- **TP53 mutations and complex cytogenetics are the strongest risk factors**
- **More patient input in the decision-making process is needed**
- **Inflammasome deserves further exploitation**

Thank you